Access DB# 78453

Point of Contact:
Thomas G. Larson, Ph.D.
703-308-7309
CM1, Rm. 6 B 01

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Delacroix Examiner #: 71100 Date: 10-22-02
Art Unit: 1614 Phone Number 30 6-3227 Serial Number: 09/308,955
Mail Box and Bldg/Room Location: 2D01 Results Format Preferred (circle): PAPER DISK E-MAIL

If mor than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): PLEASE SEE ATTACHED

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please search the method of claim 1.

Key terms are highlighted.

Also, the claimed method provisos out the use of carprofen, which is embraced by Formula (II).

Please search

Thanks

CM

Approved
T K Page
SPE, AU 1615

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CM1, Rm. 6 B 01

****

STAFF USE ONLY

Searcher: Point of Contact: Thomas G. Larson, Ph.D. 703-308-7309 CM1, Rm. 6 B 01
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: 10/25
Date Completed: 10/25
Searcher Prep & Review Time: 60
Clerical Prep Time: _____
Online Time: 147

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) 1
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN 551
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

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PTO-1590 (8-01)

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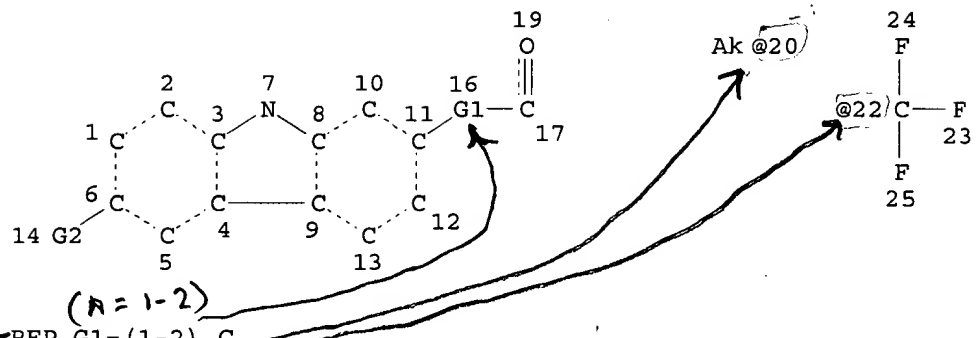

(A = 1-2)

R_2 - REP G1=(1-2) C

R_6 - VAR G2=X/NO2/20/22

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NODE ATTRIBUTES:
CONNECT IS E2  RC AT 1
CONNECT IS E2  RC AT 2
CONNECT IS E2  RC AT 5
CONNECT IS E2  RC AT 10
CONNECT IS E2  RC AT 12
CONNECT IS E2  RC AT 13
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M1-X3 C  AT 20

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L4            85 SEA FILE=REGISTRY SSS FUL L2
L5           397 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4
L6         52367 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANALGESICS+NT,PFT/CT
L8         46556 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTI-INFLAMMATORY AGENTS+NT,PF
                 T/CT
L11         9666 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "DOG (CANIS FAMILIARIS)"+NT,PF
                 T/CT
L16            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  52263-83-9/RN
L17           72 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16
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L19           69 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18
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L21          375 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L20
L22          388 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 OR L19 OR L17
L29         1563 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CYCLOOXYGENASE 2+PFT/CT
L35        92265 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 OR L8 OR L29
L36          212 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L35 AND L11
L37           16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 AND L5
L38            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L37 NOT L22
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CAL Reg# (R)-carprofen

CAS Reg# (S)+carprofen

CAS Reg# Carprofen

(w/out proviso)

(w proviso)

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=> D IBIB ABS HITSTR l37 1-16
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Display hits from L37 (w/out proviso)

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L37  ANSWER 1 OF 16  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:238754  HCAPLUS
DOCUMENT NUMBER:          137:221845
TITLE:                    Oral dosage form new animal drugs: Carprofen
AUTHOR(S):                Anon.
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These positions closed to substitution

N @ #7 open to any substitution (R9)

CO @ #17 open to any substitution (A)

Generic Ak group @ #20 limited to C1-C3 (substitutions allowed) as per

Point of Contact:
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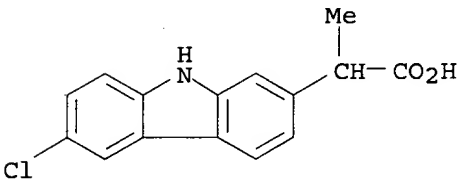
CORPORATE SOURCE: Food and Drug Administration, USA
SOURCE: Federal Register (2002), 67(31), 6865-6866, 14 Feb 2002
CODEN: FEREAC; ISSN: 0097-6326
PUBLISHER: Superintendent of Documents
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Food and Drug Administration (FDA) is amending, under the Federal Food, Drug, and Cosmetic Act the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA) filed by Pfizer, Inc. The supplemental NADA provides for a once daily, 2-mg per lb (mg/lb) dosage of carprofen, by oral chewable tablet, for the relief of pain and inflammation assocd. with osteoarthritis in dogs.

IT **53716-49-7**, Carprofen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for carprofen tablets for relief of pain and inflammation assocd. with osteoarthritis in dogs)

RN 53716-49-7 HCAPLUS

CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



L37 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:74174 HCAPLUS
DOCUMENT NUMBER: 137:163556
TITLE: Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs in canine blood
AUTHOR(S): Streppa, Heather K.; Jones, Chris J.; Budsberg, Steven C.
CORPORATE SOURCE: Department of Small Animal Medicine, College of Veterinary Medicine, University of Georgia, Athens, GA, 30602, USA
SOURCE: American Journal of Veterinary Research (2002), 63(1), 91-94
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

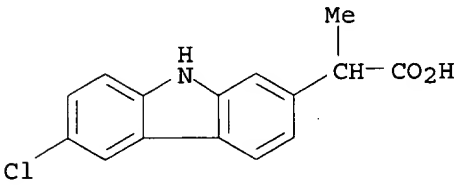
AB Cyclooxygenase (COX) selectivity of several nonsteroidal anti-inflammatory drugs (NSAIDs) was evaluated in canine blood in vitro. Nine NSAIDs were studied at 5 concns. Thromboxane B2 (TxB2) was assayed as a measure of COX-1 activity in clotted blood. Prostaglandin E2 (PGE2) was assayed as a measure of COX-2 activity in heparinized, lipopolysaccharide (LPS)-stimulated blood. All assays were competitive ELISA tests. Cyclooxygenase selectivity was expressed as a ratio of the concn. of an NSAID that inhibited 50% of the activity (IC50) of COX-1 to the IC50 of COX-2. A sep. ratio of the concn. that inhibited 80% of COX activity (IC80) was also detd. A ratio of < 1.0 indicated selectivity for COX-1, whereas a ratio of > 1.0 indicated COX-2 selectivity. Ketoprofen, aspirin, and etodolac were COX-1 selective. Piroxicam, meloxicam, and

carprofen had COX-2 selectivity. The IC50 and IC80 values were similar for most NSAIDs. This methodol. provides repeatable data from individual dogs and is comparable to results of previous in vitro and ex vivo models. Findings are also consistent with those of canine studies performed in vivo, suggesting that this is a viable in vitro assessment of the COX selectivity of NSAIDs in dogs.

IT **329900-75-6**, COX 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs (NSAIDs) in canine blood)
RN 329900-75-6 HCAPLUS
CN Synthetase, prostaglandin endoperoxide, 2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **53716-49-7**, Carprofen
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs (NSAIDs) in canine blood)
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)

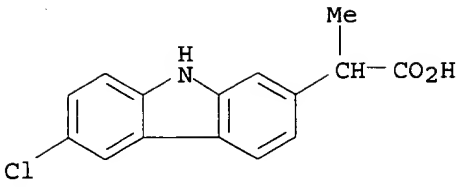


REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:34151 HCAPLUS
DOCUMENT NUMBER: 137:174632
TITLE: Oral dosage form new animal drugs; carprofen
CORPORATE SOURCE: Food and Drug Administration, USA
SOURCE: Federal Register (2001), 66(234), 63165-63166, 5 Dec 2001
CODEN: FEREAC; ISSN: 0097-6326
PUBLISHER: Superintendent of Documents
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Food and Drug Administration (FDA) is amending, under the Federal Food, Drug,and Cosmetic Act, the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA) filed by Pfizer, Inc. The supplement NADA provides for a once daily, 2-mg per lb (mg/lb) dosage of carprofen, by oral caplet, for the relief of pain and inflammation assocd. with osteoarthritis in dogs.

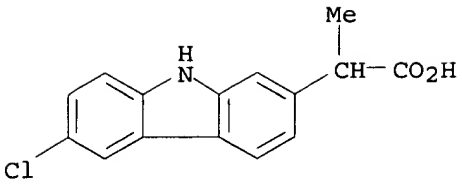
IT **53716-49-7**, Carprofen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for carprofen caplets for relief of pain and inflammation assocd. with osteoarthritis in dogs)
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



L37 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:839147 HCAPLUS
DOCUMENT NUMBER: 137:57174
TITLE: In vitro effects of cyclooxygenase inhibitors in whole blood of horses, dogs, and cats
AUTHOR(S): Brideau, Christine; Van Staden, Carlo; Chan, Chi Chung
CORPORATE SOURCE: Departments of Biochemistry & Molecular Biology, Merck Frosst Centre for Therapeutic Research, Kirkland, QC, H9R 4P8, Can.
SOURCE: American Journal of Veterinary Research (2001), 62(11), 1755-1760
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective was to det. potency and selectivity of nonsteroidal anti-inflammatory drugs (NSAID) and cyclooxygenase (COX) specific inhibitors in whole blood from horses, dogs, and cats. Activities of COX-1 and COX-2 were detd. by measuring coagulation-induced thromboxane B2 and lipopolysaccharide-induced prostaglandin E2 concns., resp., in whole blood with and without the addn. of various concns. of phenylbutazone, flunixin meglumine, ketoprofen, diclofenac, indomethacin, meloxicam, carprofen, 5-bromo-2[4-fluorophenyl]-3-[4-methylsulfonylphenyl]-thiophene (DuP 697), 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl) phenyl-2(5H)-furanone (DFU), 3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone (MF-tricyclic), and celecoxib. Potency of each test compd. was detd. by calcg. the concn. that resulted in inhibition of 50% of COX activity (IC50). Selectivity was detd. by calcg. the ratio of IC50 for COX-1 to IC50 for COX-2 (COX-1/COX-2 ratio). The novel compd. DFU was the most selective COX-2 inhibitor in equine, canine, and feline blood; COX-1/COX-2 ratios were 77.5, 74, and 69, resp. Carprofen was the weakest inhibitor of COX-2, compared with the other COX-2 selective inhibitors, and did not inhibit COX-2 activity in equine blood. In contrast, NSAID such as phenylbutazone and flunixin meglumine were more potent inhibitors of COX-1 than COX-2 in canine and equine blood. Conclusions and Clin. Relevance-The novel COX-2 inhibitor DFU was more potent and selective in canine, equine, and feline blood, compared with phenylbutazone, flunixin meglumine, and carprofen. Compds. that specifically inhibit COX-2 may result in a lower incidence of adverse effects, compared with NSAID, when administered at therapeutic dosages to horses, dogs, and cats.

IT **53716-49-7**, Carprofen
RL: PAC (Pharmacological activity); BIOL (Biological study)
(in vitro effects of cyclooxygenase inhibitors in whole blood of horses, dogs, and cats)
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)

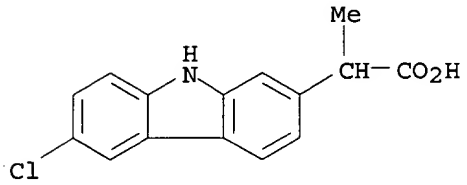


IT **329900-75-6**, Cyclooxygenase 2
RL: PAC (Pharmacological activity); BIOL (Biological study)
(inhibitors; in vitro effects of cyclooxygenase inhibitors in whole blood of horses, dogs, and cats)
RN 329900-75-6 HCAPLUS
CN Synthetase, prostaglandin endoperoxide, 2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:768723 HCAPLUS
DOCUMENT NUMBER: 137:426
TITLE: Effect of carprofen on hemostatic variables in dogs
AUTHOR(S): Hickford, Fiona H.; Barr, Stephen C.; Erb, Hollis N.
CORPORATE SOURCE: Departments of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, 14853, USA
SOURCE: American Journal of Veterinary Research (2001), 62(10), 1642-1646
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of carprofen on hemostatic variables in clin. normal dogs was evaluated. Twelve clin. normal Labrador Retrievers were used. Ten dogs (6 females, 4 males) received carprofen (2.2 mg/kg of body wt., PO, q 12 h) for 5 days. Two dogs (untreated control group; 1 female, 1 male) did not receive carprofen. Hemostatic variables (platelet count, activated partial thromboplastin time, prothrombin time, fibrinogen, platelet aggregation, and bleeding time) were assessed for all dogs prior to treatment, on day 5 of treatment, and 2 and 7 days after discontinuation of the drug (days 7 and 12). Serum biochem. variables and Hct were assessed prior to treatment and on days 5 and 12. In dogs receiving carprofen, platelet aggregation was significantly decreased, and onset of aggregation was significantly delayed on days 5, 7, and 12, compared with pretreatment values. Activated partial thromboplastin time was significantly increased on days 5, 7, and 12 over pretreatment values in treated dogs, but values remained within ref. ranges. Significant differences were not detected in buccal mucosal bleeding time, other serum biochem. and hemostatic variables, or Hct, compared with pretreatment values and the internal control group. Thus, administration of carprofen for 5 days causes minor but not clin. important alterations in hemostatic and serum biochem. variables in clin. normal Labrador Retrievers. Carprofen is commonly used to treat osteoarthritis and chronic pain in dogs, but prior to this study, its effect on platelet aggregation and hemostatic variables was unknown.
IT **53716-49-7**, Carprofen

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of carprofen on hemostatic variables in dogs)
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)

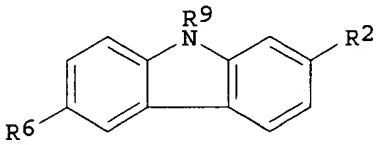


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:397826 HCAPLUS
DOCUMENT NUMBER: 135:532
TITLE: Treating or preventing the early stages of degeneration of articular cartilage or subchondral bone in mammals using carprofen and derivatives
INVENTOR(S): Evans, Nigel A.; Kilroy, Carolyn R.; Lundy, Kristin M.; Pelletier, Jean-Pierre
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001002401	A1	20010531	US 1999-283993	19990401

OTHER SOURCE(S): MARPAT 135:532
GI



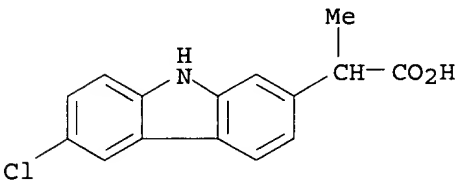
I

AB Treating or preventing the early stages of degeneration of articular cartilage or subchondral bone in the affected joint of a mammal is accomplished by administering a chondroprotective compd. I [R2 = (C(X)(Y))nC(O)A; A = OH, C1-4 alkoxy, amino, hydroxyamino, mono-(C1-2)alkylamino, di-(C1-2)alkylamino; X, Y = H, C1-2 alkyl; n = 1, 2; R6 = halo, C1-3 alkyl, CF3, nitro; R9 = H, C1-2 alkyl, Ph, phenyl-(C1-2)alkyl, (where Ph is optionally mono-substituted by F or Cl), -C(O)R (R = C1-2 alkyl, Ph, optionally mono-substituted by F or Cl), -C(O)OR' (R' = C1-2 alkyl)]. This treatment ameliorates, diminishes,

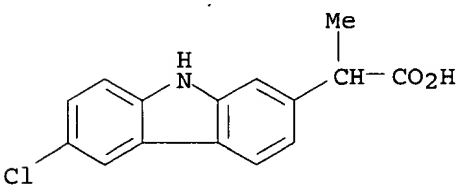
actively treats, reverses or prevents any injury, damage or loss of articular cartilage or subchondral bone subsequent to said early stage of the degeneration. Whether or not a mammal needs such treatment is detd. by whether or not it exhibits a statistically significant deviation from normal std. values in synovial fluid or membrane from the affected joint, with respect to at least five of the following substances: increased interleukin-1.beta.; increased tumor necrosis factor .alpha.; increased ratio of IL-1.beta. to IL-1 receptor antagonist protein; increased expression of p55 TNF receptors; increased interleukin-6; increased leukemia inhibitory factor; decreased insulin-like growth factor-1; decreased transforming growth factor .beta.; decreased platelet-derived growth factor; decreased basic fibroblast growth factor; increased keratan sulfate; increased stromelysin; increased ratio of stromelysin to tissue inhibitor of metalloproteases; increased osteocalcin; increased alk. phosphatase; increased cAMP responsive to hormone challenge; increased urokinase plasminogen activator; increased cartilage oligomeric matrix protein; and increased collagenase.

IT **53716-49-7**, Carprofen **53716-49-7D**, Carprofen, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carprofen and derivs. for treatment or prevention of early stages of degeneration of articular cartilage or subchondral bone)

RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



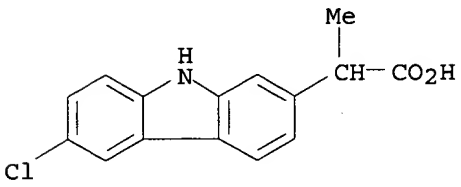
L37 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:903022 HCAPLUS
DOCUMENT NUMBER: 135:55717
TITLE: Effect of administration of nonsteroidal anti-inflammatory drugs before surgery on renal function in clinically normal dogs
AUTHOR(S): Lobetti, Remo G.; Joubert, Kenneth E.
CORPORATE SOURCE: Department of Companion Animal Medicine, University of

Pretoria, Onderstepoort, 0110, S. Afr.
SOURCE: American Journal of Veterinary Research (2000), 61(12), 1501-1507
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective was to investigate renal function in clin. normal dogs undergoing general anesthesia for ovariohysterectomies that received nonsteroidal anti-inflammatory drugs (NSAID) before surgery. 40 Clin. normal dogs were used. After induction of anesthesia, dogs were given an analgesic. Renal function was assessed before surgery and 24 and 48 h after surgery by serum urea and creatinine concns., fractional clearance of sodium (FCNa), urine .gamma.-glutamyltransferase (GGT) and alk. phosphatase (ALP) activities, and urine anal. Ten dogs in each of 4 groups received ketorolac tromethamine (0.5 mg/kg of body wt.), ketoprofen (1 mg/kg), carprofen (4 mg/kg), or morphine (0.1 mg/kg; control group). Duration of general anesthesia ranged from 1.75 to 5 h, with a mean of 3 h. Two ketorolac- and 2 ketoprofen-treated dogs had transient azotemia. A significant decrease in the FCNa between before surgery and 24 h after surgery, and between before surgery and 48 h after surgery, was found in ketoprofen- and carprofen-treated dogs. Ketorolac-, ketoprofen-, and morphine-treated dogs had a decrease in urine sp. gr. Two ketorolac-, 1 ketoprofen-, 1 carprofen-, and 4 morphine-treated dogs had increases in renal tubular epithelial cells on urine sediment examn. 24 h after surgery. In clin. normal dogs undergoing general anesthesia and elective surgery, the use of NSAID as analgesics is not contraindicated. Compared with ketorolac or ketoprofen, carprofen had the least effect on renal function and integrity.

IT **53716-49-7**, Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of administration of nonsteroidal anti-inflammatory drugs before surgery on renal function in clin. normal dogs)

RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

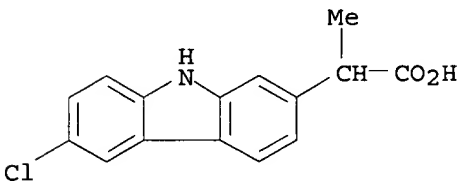
L37 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:536834 HCAPLUS
DOCUMENT NUMBER: 133:358986
TITLE: In vitro effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs
AUTHOR(S): Kay-Mugford, Patricia; Benn, Sally J.; LaMarre, Jonathan; Conlon, Peter
CORPORATE SOURCE: Department of Biomedical Sciences, Ontario Veterinary

College, University of Guelph, ON, N1G 2W1, Can.
SOURCE: American Journal of Veterinary Research (2000), 61(7), 802-810
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The differential suppressive activity of nonsteroidal anti-inflammatory drugs (NSAIDs) on canine cyclooxygenase (COX)-1 and COX-2 isoenzymes was evaluated. COX activity was detd. in the presence and absence of 4 NSAIDs (meloxicam, tolfenamic acid, carprofen, and ketoprofen), in a canine monocyte/macrophage cell line that constitutively expresses COX-1 but can be induced to express COX-2 when incubated with lipopolysaccharide. Inhibition of PGE2 synthesis by each NSAID was measured by enzyme immunoassay and attributed to specific COX-1 or COX-2 activity by assessment of COX mRNA expression by Northern blot anal. and RT-PCR. The COX selectivity of each drug was evaluated from concn.-response curves by calcg. the ratio (COX-1:COX-2) of inhibitory concns. on the basis of concns. that reduced PGE2 by 50% in each COX model. Meloxicam and tolfenamic acid preferentially inhibited COX-2, with meloxicam inhibiting COX-2 activity 12-fold more effectively than COX-1 activity. Carprofen was only 1.75-fold more selective for COX-2 than for COX-1, and ketoprofen was slightly more selective for COX-1. Thus, COX-1 and COX-2 were differentially sensitive to inhibition in vitro by NSAIDs. Meloxicam and tolfenamic acid were selective for COX-2. Carprofen and ketoprofen approached equipotency against both isoenzymes. Selective COX-2 inhibitors are a new class of drugs with anti-inflammatory effects similar to those of conventional NSAIDs but with fewer adverse effects. Development of these agents for veterinary use would be facilitated by the convenience of using a canine cell line as a model system to screen COX-1 and COX-2 inhibitor activities in vitro.

IT **53716-49-7**, Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(nonsteroidal anti-inflammatory drugs selective inhibition of cyclooxygenase isoforms in dog monocytes/macrophages)

RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

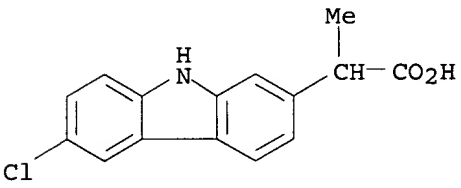
L37 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:718417 HCAPLUS
DOCUMENT NUMBER: 132:189456
TITLE: Carprofen inhibition of flare in the dog measured by laser flare photometry
AUTHOR(S): Krohne, Sheryl G.; Blair, Michael J.; Bingaman, David; Gionfriddo, Juliet R.

CORPORATE SOURCE: Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Purdue University, West Lafayette, IN, 47907, USA
SOURCE: Veterinary Ophthalmology (1998), 1(2-3), 81-84
CODEN: VEOPF7; ISSN: 1463-5216
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to det. whether oral carprofen (Rimadyl) treatment in dogs could prevent or decrease the breakdown of the blood-aq. barrier. The topical pilocarpine irritative model was used to induce breakdown and cause flare. Pilocarpine was instilled in both eyes of seven dogs at time zero and again 5 h later. At 7 h, laser flare photometry was used to measure the flare concn. in each eye using the Kowa FC-1000 laser flare cell meter. All treatments were then discontinued. Two days later, carprofen was administered to the same dogs for a total of three doses. After the last dose of carprofen, pilocarpine treatments and flare measurements were repeated. Carprofen pretreatment resulted in a 68% inhibition of flare, which was highly significant ($P < 0.01$). The pilocarpine group had a mean of 16.1 photon counts per ms (PC ms-1) .+-. 2.2 SE, and the carprofen group had a mean of 7.0 PC/ms .+-. 1.2 SE. These results compare favorably with previous studies measuring increased protein or fluorescein concns. in the aq. humor after blood-aq. barrier breakdown in the dog. These results suggest that carprofen may be effectively used as a systemically administered ocular anti-inflammatory drug. Carprofen has the added benefit of fewer reported side effects.

IT **53716-49-7**, Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carprofen inhibition of flare in dog: relevance for antiinflammatory action)

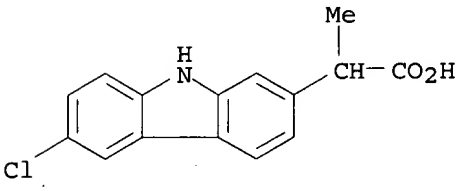
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:466481 HCAPLUS
DOCUMENT NUMBER: 131:204446
TITLE: Oral dosage form new animal drugs; carprofen
CORPORATE SOURCE: Food and Drug Administration, HHS, Center for Veterinary Medicine (HFV-110), Food and Drug Administration, Rockville, MD, 20855, USA
SOURCE: Federal Register (1999), 64(115), 32180-32181, 16 Jun 1999
CODEN: FEREAC; ISSN: 0097-6326
PUBLISHER: Superintendent of Documents

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Food and Drug Administration (FDA) is amending, under the Federal Food, Drug, and Cosmetic Act, the animal drug regulations to reflect approval of a new animal drug application (NADA) filed by Pfizer, Inc. The NADA provides for veterinary prescription use of carprofen chewable tablets for the relief of pain and inflammation assocd. with osteoarthritis in dogs.
IT **53716-49-7**, Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for carprofen chewable tablets for treatment of osteoarthritis in dogs)
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



L37 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:744944 HCAPLUS
DOCUMENT NUMBER: 130:10625
TITLE: COX-2-selective carprofen and related compounds for treating pain and inflammation in dogs
INVENTOR(S): Lundy, Kristin Marie; Ricketts, Anthony Paul
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9850033	A1	19981112	WO 1998-IB662	19980501
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9869321	A1	19981127	AU 1998-69321	19980501
EP 988034	A1	20000329	EP 1998-915041	19980501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
BR 9808720	A	20000711	BR 1998-8720	19980501
JP 2000513020	T2	20001003	JP 1998-547869	19980501

Appl.

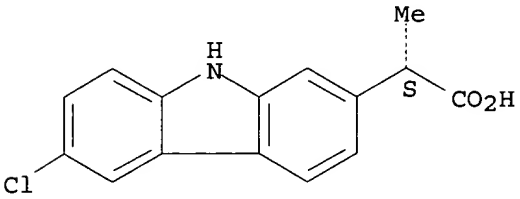
ZA 9803722 A 19991104 ZA 1998-3722 19980504
PRIORITY APPLN. INFO.: US 1997-45635P P 19970505
WO 1998-IB662 W 19980501
OTHER SOURCE(S): MARPAT 130:10625

AB The invention relates to treating or preventing inflammatory processes and diseases in dogs assocd. with the activity of inducible cyclooxygenase-2 (COX-2), while at the same time reducing or eliminating undesirable side effects assocd. with simultaneous inhibition of the activity of constitutive cyclooxygenase-1 (COX-1) by selectively inhibiting COX-2 activity with ref. to COX-1 activity, wherein the selectivity ratio or COX-2:COX-1 activity inhibition is at least 3:1 based on ex vivo inhibition levels measured in whole blood. The inhibitor is a member selected from the group of antiinflammatory compds. consisting essentially of salicylic acid derivs., p-aminophenol derivs., indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, and alkanones; the inhibitor in particular is comprised of the (+)(S)-enantiomer of 6-chloro-.alpha.-methyl-9H-carbazole-2-acetic acid.

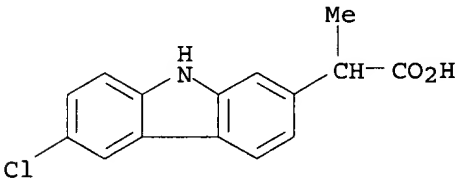
IT **52263-84-0**, (S)-Carprofen **53716-49-7**, Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2-selective carprofen and related compds. for treating pain and inflammation in dogs)

RN 52263-84-0 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl-, (.alpha.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



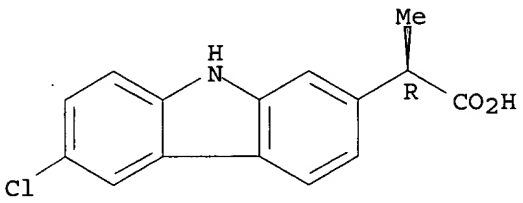
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



IT **52263-83-9**, (R)-Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2-selective carprofen and related compds. for treating pain and inflammation in dogs, and comparative inhibition of COX-1 and -2 by carprofen and other NSAIDs)

RN 52263-83-9 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl-, (.alpha.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



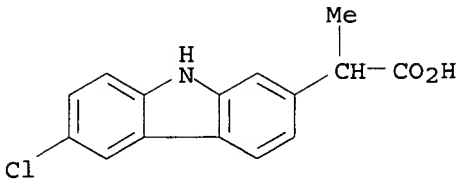
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:439600 HCAPLUS
DOCUMENT NUMBER: 129:211405
TITLE: Hepatocellular toxicosis associated with administration of carprofen in 21 dogs
AUTHOR(S): Macphail, Catriona M.; Lappin, Michael R.; Meyer, Dennis J.; Smith, Steven G.; Webster, Cynthia R. L.; Armstrong, P. Jane
CORPORATE SOURCE: Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, 80523, USA
SOURCE: Journal of the American Veterinary Medical Association (1998), 212(12), 1895-1901
CODEN: JAVMA4; ISSN: 0003-1488
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Carprofen is a drug approved for use in dogs that has provided an alternative method of treatment for dogs with chronic osteoarthritis. However, as with any nonsteroidal anti-inflammatory drug, there is potential for gastrointestinal tract, renal, and hepatic problems. Carprofen-assocd. hepatic toxicosis is believed to be idiosyncratic and host dependent. Clin. signs assocd. with carprofen-induced hepatic toxicosis include inappetence, vomiting, and icterus. Assocd. biochem. abnormalities include increased serum activities of hepatic enzymes and hyperbilirubinemia. Most dogs recover uneventfully after discontinuation of carprofen and administration of supportive care.

IT **53716-49-7**, Carprofen
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hepatocellular toxicosis assocd. with administration of carprofen in dogs)

RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)

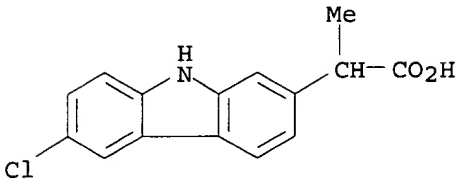


L37 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:194180 HCAPLUS
DOCUMENT NUMBER: 126:233297
TITLE: Effect of carprofen on sulfated glycosaminoglycan metabolism, protein synthesis, and prostaglandin release by cultured osteoarthritic canine chondrocytes
AUTHOR(S): Benton, Hilary P.; Vasseur, Philip B.; Broderick-Villa, Gregory A.; Koolpe, Mitchell
CORPORATE SOURCE: Departments of Anatomy, Physiology and Cell Biology, School of Veterinary Medicine, University of California, Davis, CA, 95616, USA
SOURCE: American Journal of Veterinary Research (1997), 58(3), 286-292
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

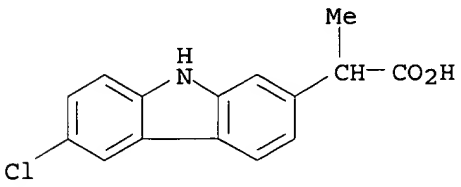
AB We detd. whether the nonsteroidal anti-inflammatory drug carprofen directly influences canine chondrocyte metab. Cartilage from the femoral heads of 13 dogs undergoing total hip replacement was used. Rates of glycosaminoglycan (GAG) synthesis and degrdn., protein synthesis, cell viability, and prostaglandin release were detd. in canine explant cartilage or monolayer canine chondrocyte cultures in the presence of 0 to 100 .mu.g of carprofen/mL. Rate of GAG synthesis was assessed as incorporation of [35S]sulfate into cartilage matrix during a 3-h pulse label. Degrdn. of cartilage GAG was assessed as rate of release of [35S]sulfate from prelabeled explant cultures. Rates of total protein synthesis were assessed as incorporation of [35S]methionine into trichloracetic acid precipitable material during a 3-h pulse label. Radiolabeled chondrocyte proteins were sepd. by polyacrylamide gel electrophoresis and visualized by fluorog.. Rates of prostaglandin E2 release were assessed by RIA. Carprofen stimulated a significant increase in the rate of GAG synthesis at concns. of 1 and 10 .mu.g/mL, with no change in total protein synthesis, pattern of new protein synthesis, or cell viability. At concn. .gtoreq. 20 .mu.g/mL, inhibition of GAG synthesis and total protein synthesis was obsd. There was no significant change in rate of release of GAG from cartilage explants, but potent inhibition of prostaglandin release was obsd. Carprofen has a direct influence on chondrocyte activity, resulting in changes in rate of prodn. of cartilage matrix. In detg. the optimal therapeutic dose of carprofen for arthritic conditions in dogs, it is important to consider potential influences on cartilage, as well as anti-inflammatory actions.

IT **53716-49-7**, Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carprofen effect on sulfated glycosaminoglycan metab., protein synthesis, and prostaglandin release by osteoarthritic canine chondrocytes)

RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



L37 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:39638 HCAPLUS
DOCUMENT NUMBER: 126:79805
TITLE: Oral dosage form new animal drugs; carprofen caplets
CORPORATE SOURCE: Food Drug Administration, Rockville, MD, 20855, USA
SOURCE: Federal Register (1996), 61(244), 66581, 18 Dec 1996
CODEN: FEREAC; ISSN: 0097-6326
PUBLISHER: Superintendent of Documents
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nonsteroidal anti-inflammatory carprofen caplets may be used orally in dogs for relief of pain and inflammation, under the Federal Food, Drug, and Cosmetic Act. Carprofen has been shown to be clin. effective for the relief of signs assocd. with osteoarthritis.
IT **53716-49-7**, Carprofen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for oral carprofen caplets for relief of pain and inflammation in dogs)
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



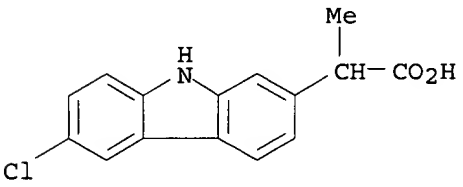
L37 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:498947 HCAPLUS
DOCUMENT NUMBER: 122:281714
TITLE: Randomized, controlled trial of the efficacy of carprofen, a nonsteroidal anti-inflammatory drug, in the treatment of osteoarthritis in dogs
AUTHOR(S): Vasseur, Philip B.; Johnson, Ann L.; Budsberg, Steve C.; Lincoln, James D.; Toombs, James P.; Whitehair, Jon G.; Lentz, Ellen L.
CORPORATE SOURCE: School of Veterinary Medicine, University of California, Davis, CA, 95616, USA
SOURCE: Journal of the American Veterinary Medical Association

(1995), 206(6), 807-11
CODEN: JAVMA4; ISSN: 0003-1488
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Seventy dogs were included in a randomized, controlled, multicenter trial to test the efficacy of carprofen (2.2 mg/kg of body wt., PO, q 12 h) for relief of clin. signs assocd. with osteoarthritis. Thirty-six dogs received carprofen, and 34 received a placebo. Response of the dogs was evaluated by comparing results of force plate examn. and a graded lameness examn. performed before and immediately after 2 wk of treatment, and by obtaining a subjective assessment of the dog's posttreatment condition from owners and participating veterinarians. A phys. examn., CBC, serum biochem. analyses, urinalysis, and fecal occult blood test were performed before and after treatment to monitor safety. For force plate evaluation, the odds ratio was 3.3, meaning that a dog treated with carprofen was 3.3 times more likely to have a pos. response than was a dog treated with the placebo. For evaluation by a veterinarian, the odds ratio was 3.5, and for owner evaluation, the odds ratio was 4.2. Institution where dogs were treated did not have a significant effect on results. A variety of reactions that may have been related to the medication (placebo or carprofen) were recorded; however, none were considered serious. Serum alanine aminotransferase activity was high in 3 dogs (2 that received placebo and 1 that received carprofen) at the conclusion of treatment; none of the 3 dogs were clin. ill. Ten dogs (5 that received placebo and 5 that received carprofen) had neg. pretreatment and pos. posttreatment fecal occult blood test results.

IT **53716-49-7**, Carprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory activity of carprofen in osteoarthritis in dogs)

RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



L37 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:368073 HCAPLUS
DOCUMENT NUMBER: 122:255754
TITLE: Stereospecific pharmacodynamics and pharmacokinetics of carprofen in the dog
AUTHOR(S): McKellar, Q. A.; Delatour, P.; Lees, P.
CORPORATE SOURCE: Veterinary School, University of Glasgow, Glasgow, G61 1QH, UK
SOURCE: Journal of Veterinary Pharmacology and Therapeutics (1994), 17(6), 447-54
CODEN: JVPTD9; ISSN: 0140-7783
DOCUMENT TYPE: Journal
LANGUAGE: English

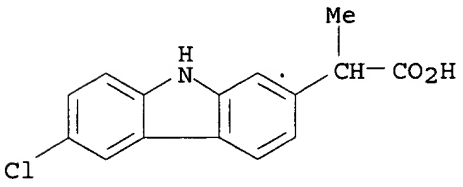
AB The non-steroidal anti-inflammatory drug (NSAID) carprofen (CPF) contains

a single chiral center. It was administered orally to Beagle dogs as a racemate (rac-CPF) at a dose of 4 mg per kg body wt. and as individual (-)(R) and (+)(S) enantiomers at 2 mg per kg body wt. Each of the enantiomers achieved similar plasma bioavailability following administration as the racemate as they did following their sep. administration. Only the administered enantiomers were detectable when the drug was given in the (-)(R) or (+)(S) form, indicating that chiral inversion did not occur in either direction. Higher plasma concns. of the (-)(R) (Cmax 18 .mu.g/mL, AUC0-24 118 .mu.g h/mL) than the (+)(S) (Cmax 14 .mu.g/mL, AUC0-24 67 .mu.g h/mL) enantiomer were achieved following administration of the racemate. Both enantiomers distributed into peripheral s.c. tissue cage fluids, but Cmax and AUC values were lower for both transudate (non-stimulated tissue cage fluid) and exudate (induced by the intracaveal administration of the irritant carrageenan) than for plasma. Drug concns. in transudate and exudate were similar, as indicated by Cmax and AUC values, although CPF penetrated more rapidly into exudate than into transudate. Neither rac-CPF nor either enantiomer inhibited thromboxane B2 (T .times. B2) generation by platelets in clotting blood (serum T .times. B2), or prostaglandin E2 (PGE2) and 12-hydroxyeicosatetraenoic acid (12-HETE) synthesis in inflammatory exudate. Since other studies have shown that rac-CPF at the 4 mg/kg dose rate possesses analgesic and anti-inflammatory effects in the dog, it is concluded that the principal mode of action of the drug must be by mechanisms other than cyclooxygenase or 12-lipoxygenase inhibition.

IT **53716-49-7**, Carprofen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(racemic; stereospecific pharmacodynamics and pharmacokinetics of carprofen in dog in relation to mechanism of antiinflammatory activity)

RN 53716-49-7 HCAPLUS

CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)

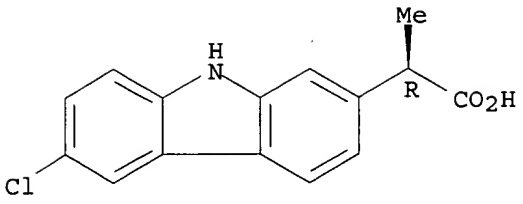


IT **52263-83-9 52263-84-0**, (S)+Carprofen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(stereospecific pharmacodynamics and pharmacokinetics of carprofen in dog in relation to mechanism of antiinflammatory activity)

RN 52263-83-9 HCAPLUS

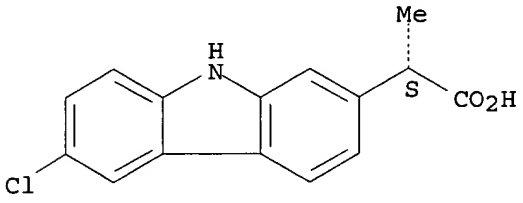
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl-, (.alpha.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

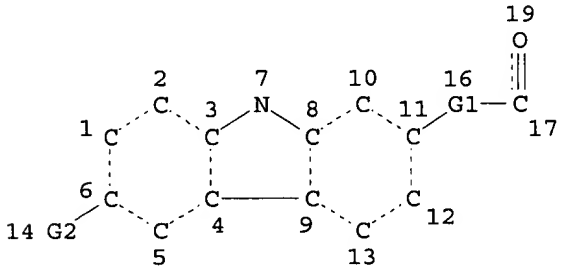


RN 52263-84-0 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl-, (.alpha.S)- (9CI) (CA INDEX NAME)

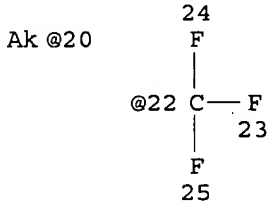
Absolute stereochemistry.



=> d que l39
L2 STR



Same structure as before



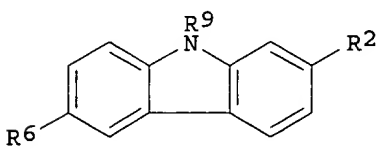
REP G1=(1-2) C
VAR G2=X/NO2/20/22
NODE ATTRIBUTES:
CONNECT IS E2 RC AT 1
CONNECT IS E2 RC AT 2
CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 10
CONNECT IS E2 RC AT 12
CONNECT IS E2 RC AT 13
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS M1-X3 C AT 20

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L4 85 SEA FILE=REGISTRY SSS FUL L2

this search checks to see if any documents were lost that contained derivatives of carprofen when the hits containing carprofen were removed in L38 above,

```
L5          397 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4
L6        52367 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANALGESICS+NT,PFT/CT
L8        46556 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTI-INFLAMMATORY AGENTS+NT,PF
                T/CT
L11        9666 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "DOG (CANIS FAMILIARIS)"+NT,PF
                T/CT
L24          24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  53716-49-7D OR 52263-84-0D OR
                52263-83-9D
L29        1563 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CYCLOOXYGENASE 2+PFT/CT
L35       92265 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 OR L8 OR L29
L36         212 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L35 AND L11
L37          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 AND L5 (w/o proviso)
L39           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L37 AND L24 (w proviso)


=> d que l40
L11        9666 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "DOG (CANIS FAMILIARIS)"+NT,PF
                T/CT
L24          24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  53716-49-7D OR 52263-84-0D OR
                52263-83-9D
L40           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 AND L11 (w proviso)


=> s l39 or l40
L41           1 L39 OR L40      same hit

=> D IBIB ABS HITSTR

L41  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:397826  HCAPLUS
DOCUMENT NUMBER:          135:532
TITLE:                    Treating or preventing the early stages of
                          degeneration of articular cartilage or subchondral
                          bone in mammals using carprofen and derivatives
INVENTOR(S):              Evans, Nigel A.; Kilroy, Carolyn R.; Lundy, Kristin
                          M.; Pelletier, Jean-Pierre
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 24 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     US 2001002401      A1   20010531       US 1999-283993   19990401
OTHER SOURCE(S):          MARPAT 135:532
GI
```



I

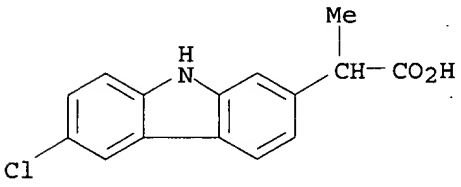
Look for derivatives of carprofen use same reg # as in L16, L18, & 2 but with "D" added (Note L22 above).

Search derivatives directly using only CAS Reg #s.

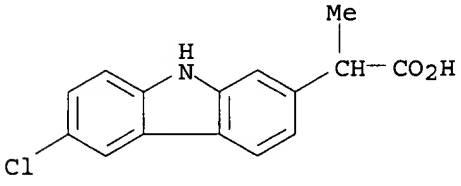
AB Treating or preventing the early stages of degeneration of articular cartilage or subchondral bone in the affected joint of a mammal is accomplished by administering a chondroprotective compd. I [R2 = (C(X)(Y))nC(O)A; A = OH, C1-4 alkoxy, amino, hydroxyamino, mono-(C1-2)alkylamino, di-(C1-2)alkylamino; X, Y = H, C1-2 alkyl; n = 1, 2; R6 = halo, C1-3 alkyl, CF3, nitro; R9 = H, C1-2 alkyl, Ph, phenyl-(C1-2)alkyl, (where Ph is optionally mono-substituted by F or Cl), -C(O)R (R = C1-2 alkyl, Ph, optionally mono-substituted by F or Cl), -C(O)OR' (R' = C1-2 alkyl)]. This treatment ameliorates, diminishes, actively treats, reverses or prevents any injury, damage or loss of articular cartilage or subchondral bone subsequent to said early stage of the degeneration. Whether or not a mammal needs such treatment is detd. by whether or not it exhibits a statistically significant deviation from normal std. values in synovial fluid or membrane from the affected joint, with respect to at least five of the following substances: increased interleukin-1.beta.; increased tumor necrosis factor .alpha.; increased ratio of IL-1.beta. to IL-1 receptor antagonist protein; increased expression of p55 TNF receptors; increased interleukin-6; increased leukemia inhibitory factor; decreased insulin-like growth factor-1; decreased transforming growth factor .beta.; decreased platelet-derived growth factor; decreased basic fibroblast growth factor; increased keratan sulfate; increased stromelysin; increased ratio of stromelysin to tissue inhibitor of metalloproteases; increased osteocalcin; increased alk. phosphatase; increased cAMP responsive to hormone challenge; increased urokinase plasminogen activator; increased cartilage oligomeric matrix protein; and increased collagenase.

IT **53716-49-7**, Carprofen **53716-49-7D**, Carprofen, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carprofen and derivs. for treatment or prevention of early stages of degeneration of articular cartilage or subchondral bone)

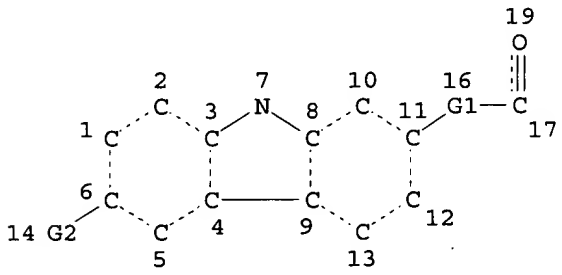
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



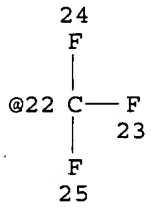
RN 53716-49-7 HCAPLUS
CN 9H-Carbazole-2-acetic acid, 6-chloro-.alpha.-methyl- (9CI) (CA INDEX NAME)



```
=> FIL BEILSTEIN
FILE 'BEILSTEIN' ENTERED AT 13:20:05 ON 25 OCT 2002
COPYRIGHT (c) 2002 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften
licensed to Beilstein Chemiedaten & Software GmbH and MDL Information Systems GmbH

FILE RELOADED ON OCTOBER 20, 2002

FILE COVERS 1779 TO 2001.
*** FILE CONTAINS 8,374,887 SUBSTANCES ***

>>> For the revised summary sheet please see:
    http://info.cas.org/ONLINE/DBSS/beilsteinss.html <<<

>>> PLEASE NOTE: Reaction and substance documents are stored in
    different file segments. Use separate queries to search for
    reaction and substance data. When searching for bibliographic
    information you have the option to chose the file segment.
    (Use "/XXX.SUB" to search for a bibliographic term in
    substance documents. To restrict the search to reaction
    documents use "/XXX.RX".)
    For additional information see HELP RXS. <<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE  <<<

**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                 *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE    *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE           *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                         *
* FOR PRICE INFORMATION SEE HELP COST                                 *
**********************************************************************

=> d que l49
L2                STR
```



Ak @20



Same Structure as used in previous searches.

```
REP G1=(1-2) C
VAR G2=X/NO2/20/22
NODE ATTRIBUTES:
CONNECT IS E2  RC AT   1
CONNECT IS E2  RC AT   2
CONNECT IS E2  RC AT   5
CONNECT IS E2  RC AT  10
CONNECT IS E2  RC AT  12
CONNECT IS E2  RC AT  13
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
```

```
ECOUNT  IS M1-X3 C  AT  20

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L4            85 SEA FILE=REGISTRY SSS FUL L2
L43           41 SEA FILE=BEILSTEIN SSS FUL L2
L44           30 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L4
L45           11 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L43 NOT L44
L49            0 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L45 AND (CANINE OR CANIS OR
                 DOG OR HUND)
```

Hit structures in Beilstein but not in Registry

("dog" in German)

```
=> d his l47

     (FILE 'BEILSTEIN' ENTERED AT 13:09:26 ON 25 OCT 2002)
L47          ANALYZE L45 1-11 BSO :          3 TERMS
```

BSO - Beilstein source

All 11 structures are from only 3 documents. It is expensive to print references from Beilstein. I can print these if you would like to see them. Please let me know.